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Catalytic asymmetric addition of alkynylzinc reagents to ketones using polymer-supported chiral Schiff-base amino alcohols

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Abstract—Polymer-supported Schiff-base of optically active amino alcohols was used as chiral ligands in the enantioselective addition of alkynylzinc to simple ketones. At a 10 mol % ligand loading, chiral propargylic alcohols with moderate to good ee values (up to 89%) were produced. The polymeric catalyst could be recycled many times and used for further reactions.

1. Introduction

Organic reactions using polymer-supported catalysts have received much attention because of their practical advantages.[1] This strategy has a built-in advantage due to the ease of separation of the catalyst from the reaction system by simple filtration. In addition, the recovered catalyst can be reused several times to save precious materials. Recently, a number of excellent ligands have been employed for the asymmetric alkynylation of aldehydes[2] and ketones.[3] However, the use of carbonyl compounds as alkynyl group acceptors catalyzed by polymer-supported catalysts is still a formidable challenge.

Degni et al.[4a] reported an asymmetric alkynylation of aldehydes in the presence of polymer-supported L-prolinol **1** and $Zn(OTf)_2$.[4] Until recently, only one reference reported a polymeric Zn(salen) **2**, which could catalyze the enantioselective addition of alkynylzincs to ketones with moderate ee values.[5] Although the pioneering work has been described by Abdi et al., the design and development of easily accessible and economical chiral ligands is still a worthwhile project. As part of our ongoing studies into the application of Schiff-base amino alcohol **3**[6d] to promote the asymmetric addition of alkynylzincs to ketones,[6] we herein report an example of the polymer supported catalytic system for the enantioselective addition of alkynylzinc to ketones. This system does not require the addition of other Lewis acids except diethylzinc and the necessity to prepare the alkynylzinc reagent separately (Fig. 1).

2. Results and discussion

Four polymer-supported ligands **6a** and **6b** and **9a** and **9b** were prepared by grafting of Schiff-base amino alcohols **5** and **8** onto the Merrifield resin as described in Scheme 1, and the catalyst loading was based on elemental nitrogen analysis (see Section 4.2). Initially, we examined the performances of catalysts **6a**, **6b**, **9a** and **9b**, at a 10 mol % loading in the presence of 0.5 equiv Et_2Zn. The addition reaction proceeded smoothly in toluene at room temperature for 14 h to afford propargylic alcohols in good to excellent yields (Table 1, entries 1–4). The polymer-supported Schiff-base amino alcohol **9a** was found to be the best ligand in our studies. We also found this reaction to be strongly influenced by the reaction solvent. The best enantiomeric excess (ee) value could be obtained in toluene, while low ee value was found with CH_2Cl_2 as a solvent (Table 1, entry 6).[7] Next, we tested the different catalyst loading. When the amount of **9a** was reduced to 5 mol % and 1 mol %, the enantiomeric excesses were decreased to 54% and 42% (Table 1, entries 7 and 8), and the reaction became very slow when the amount of **9a** was 1 mol % (Table 1, entry 8). Temperature also made a significant impact on the ee values of the propargylic alcohols

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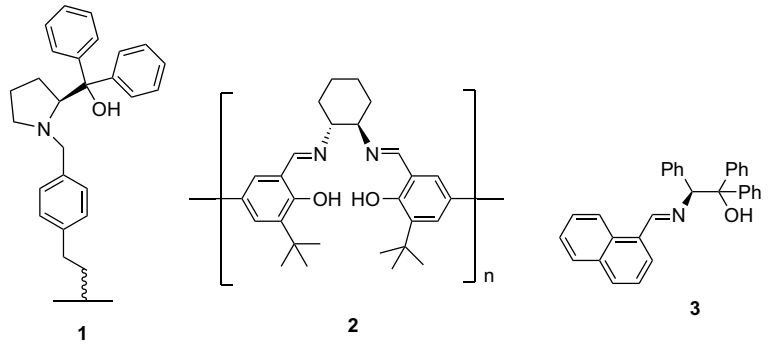
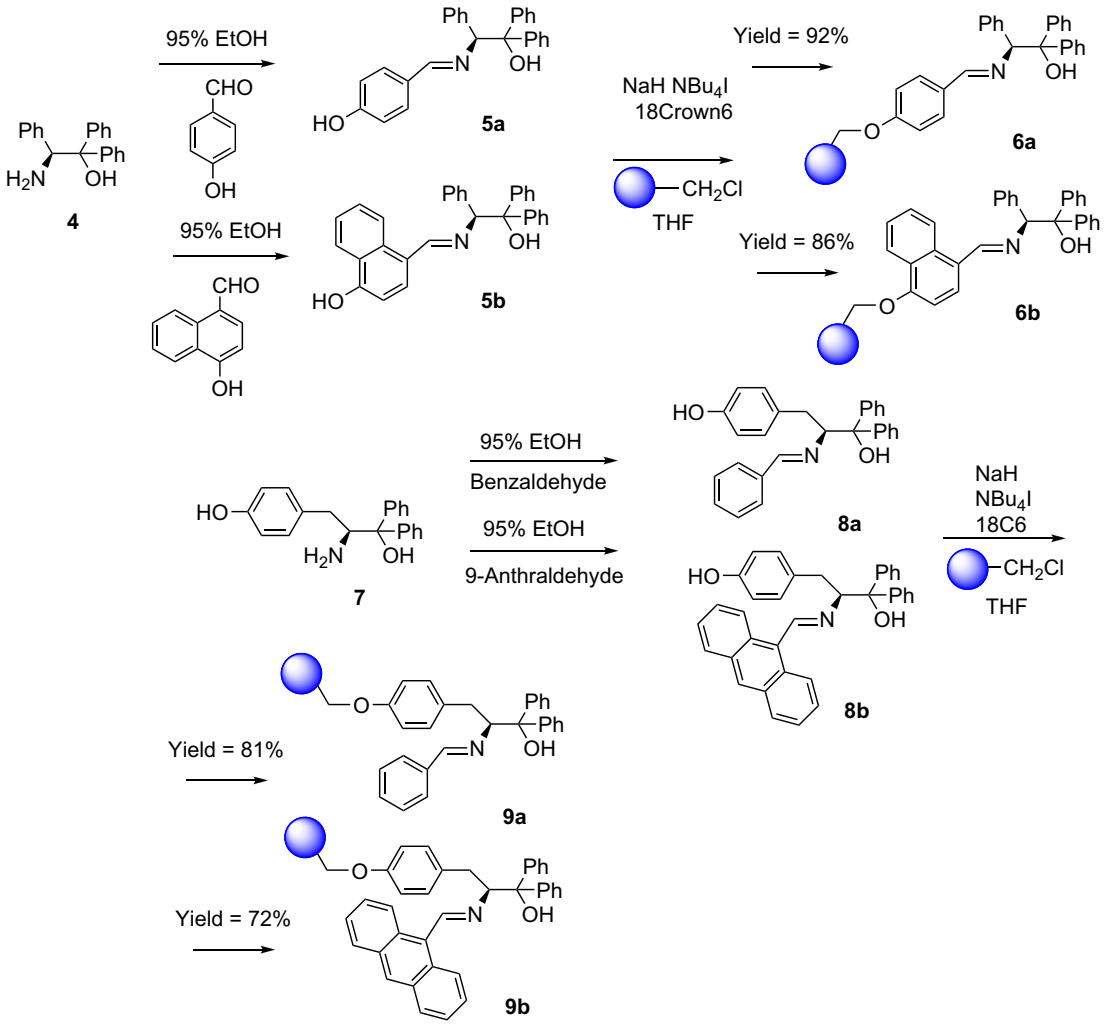


Figure 1.

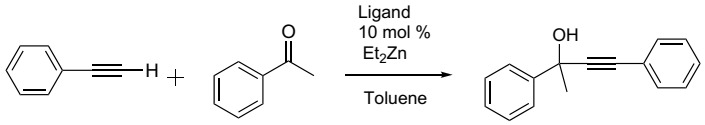


Scheme 1. Synthesis of polymer-supported ligands **6** and **9** from amino alcohols **5** and **8**.

produced. Decreasing the temperature from room temperature to 0 °C led to an increase in ee value (Table 1, entries 3, 12, and 13), while the best ee value was obtained by conducting the reaction at −18 °C. When the amount of Et_2Zn was increased from 1.2 equiv to 4 equiv, the ee changed only slightly (Table 1, entries 2, 9–11).

Having established the optimal reaction conditions for the enantioselective alkynylation of acetophenone, we decided to screen a series of aromatic ketones to evaluate the scope of this reaction. Substrates bearing substituents at the *ortho*-positions were known to have a significant effect on the ee of the products. 2′-Methoxyacetophenone and 2′-

Table 1. Reaction optimization for the addition of phenylacetylene to ketones[a]



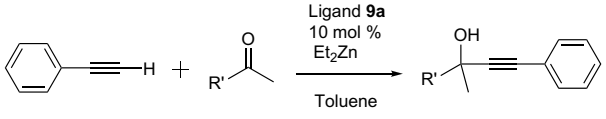
Entry	Ligand	Mol %	Solvent	T (°C)	Time (h)	Et_2Zn[b] (mL)	ee[c] (%)	Yield[d] (%)
1	**6a**	10	Toluene	rt	14	0.5	53	82
2	**6b**	10	Toluene	rt	14	0.5	45	75
3	**9a**	10	Toluene	rt	14	0.5	63	83
4	**9b**	10	Toluene	rt	14	0.5	51	88
5	**9a**	10	Hexane	rt	14	0.5	53	90
6	**9a**	10	CH_2Cl_2	rt	14	0.5	10	65
7	**9a**	5	Toluene	rt	14	0.5	54	75
8	**9a**	1	Toluene	rt	36	0.5	42	61
9	**9a**	10	Toluene	rt	14	0.3	60	78
10	**9a**	10	Toluene	rt	14	0.75	61	85
11	**9a**	10	Toluene	rt	14	1.0	58	88
12	**9a**	10	Toluene	0	24	0.5	70	74
13	**9a**	10	Toluene	−18	72	0.5	75	65

[a] Unless otherwise specified, the reactions were run under argon in 1 mL solvent at room temperature with 1 M Et_2Zn.
[b] 1 M Et_2Zn in toluene.
[c] The enantiomeric excess was determined by HPLC on Chiralcel OD-H column.
[d] Yield of isolated product.

fluoroacetophenone gave products with 63% and 89% ees, respectively (Table 2, entries 1 and 5). However, the electronic influence of the *para*-substituents also had an impact on the product ee values (entries 4, 7–9). When an α,β-unsaturated ketone was used as the substrate, the corresponding product was obtained with an ee value of 53%.[8] The unsatisfactory ee values of aliphatic ketones compared to aromatic ketones may be due to the steric factors. The catalytic results of **9a** were all decreased as compared to its homogeneous system. This might partly be ascribed to the competitive background reaction of alkynylzinc reagents to ketones[9] (Table 3).

The catalytic capability of polymer-supported Schiff-base amino alcohols was retained in successive reaction cycles. The addition of alkynylzinc to ketones in the presence of ligand **9a** gave the addition product with an ee value of 73% in the fourth and 70% in the fifth reaction cycle. These results implied that the polymer-supported Schiff-base amino alcohol **9a** possessed the advantage of ready reusability in the consecutive asymmetric addition of alkynylzincs to ketones. However, when further recycling was performed, the reaction became very slow. We monitored the hydrolysis of Schiff-base during the catalyst recovery.

Table 2. Asymmetric addition of phenylacetylene to aromatic ketones using polymer-supported Schiff-base amino alcohol **9a**[a,b,c,d]



Entry	Ketones	Ligand (mol %)	ee (%)	Yield (%)
1	2′-Fluoroacetophenone	10	89	65
2	2′-Naphthacetophenone	10	80	71
3	1′-Naphthacetophenone	10	80	64
4[e]	4′-Methoxyacetophenone	10	73	70
5[e]	2′-Methoxyacetophenone	10	62	58
6	3′-Methylacetophenone	10	73	68
7	4′-Methylacetophenone	10	73	69
8	4′-Fluoroacetophenone	10	70	71
9	4′-Chloroacetophenone	10	73	74
10	Benzalacetone	10	53	65

[a] All of the entries: ligand/Et_2Zn/phenylacetylene/ketones = 0.1:2:2:1.
[b] Unless otherwise specified, the reactions were run under argon in 1 mL toluene at −18 °C for 72 h.
[c] The enantiomeric excess was determined by HPLC on Chiralcel OD-H column.
[d] Yield of isolated product.
[e] The reaction was performed for 90 h.

Table 3. Asymmetric addition of alkynylzinc to ketone using the recycled polymer-supported catalyst **9a**

Ketones	Run (no.)	ee (%)	Yield (%)
Acetophenone	1	75	65
Acetophenone	2	75	64
Acetophenone	3	74	60
Acetophenone	4	73	60
Acetophenone	5	70	50

3. Conclusion

In conclusion, we have developed a catalytic asymmetric alkynylation of ketones promoted by polymer-supported Schiff-base amino alcohols. The main features of this asymmetric reaction are as follows: (1) The ligand could be recycled by a simple filtration and the recovered catalyst may be reused. (2) Catalyst **9a** could be reused successfully in the successive additions of alkynylzinc to ketones. Although the propargylic alcohols showed moderate to good ee values, the reusability of such polymer-supported Schiff-base amino alcohols could lead to more efficient and environmentally benign processes.

4. Experimental

All reactions were carried out under an argon atmosphere and solvents were dried according to established procedures. Reactions were monitored by thin layer chromatography (TLC). Column chromatography purifications were carried out using silica gel. All ketones and amino acids were purchased from Acros or Fluka. Diethylzinc was prepared from EtI with Zn, and then was diluted with hexane and toluene to 1.0 M. Melting points were recorded on X-4 melting point apparatus and the thermometer was uncorrected. NMR spectra were measured on AM 400 Hz spectrometers and DRX-200 MHz spectrometers (with TMS as an internal standard). IR spectra were obtained on Nicolet NEXUS 670 FT-IR. Optical rotations were recorded on a Perkin–Elmer 341 polarimeter. The ESI-MS was recorded on a Mariner biomassspectrometer. The ee value determination was carried out using chiral HPLC with a Daicel Chiracel OD-H column on Waters with a 996 UV-detector.

4.1. Preparation of Schiff-base amino alcohols 5a, 5b, 8a and 8b

General procedure for the preparation of Schiff-base amino alcohols **5a**, **5b** and **7**: To a solution of amino alcohol (4 mmol) in 30 mL of 95% EtOH was added the aldehyde (4 mmol). The resulting solution was stirred for 24 h at room temperature and then the reaction was vacuum filtered to provide the Schiff-base amino alcohol.[6d]

4.1.1. 4-((*E*)-((*S*)-2-Hydroxy-1,2,2-triphenylethylimino)-methyl)phenol 5a. Mp 164 °C; $[\alpha]_D^{18} = -241$ (*c* 4.3, THF); ^{1}H NMR (400 MHz, DMSO-d_6); δ 8.27 (s, 1H, CH=N), 7.71–7.69 (d, 1H, $J = 8$ Hz), 7.66–7.64 (d, 1H, $J = 8$ Hz), 7.54–7.52 (m, 2H), 7.37–7.32 (m, 3H), 7.30–7.11 (m, 5H), 7.09–6.90 (m, 6H), 6.72–6.70 (m, 2H). 5.00 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.6, 160.0, 167.4, 145.7, 129.9, 129.4, 128.9, 127.9, 127.0, 126.9, 126.2, 126.0, 125.9, 125.8, 125.5, 115.2, 61.1. IR (KBr): 3470, 3358, 3026, 1638, 1604, 1449, 1259, 1056, 748, 697 cm^{-1}; MS (ESI): *m*/*z*: 394.3 $[M+H]^+$, 416 $[M+Na]^+$. Anal. Calcd for $C_{27}H_{23}NO_2$: C, 82.42; H, 5.89; N, 3.56. Found: C, 82.07; H, 5.90; N, 3.47.

4.1.2. 4-((*E*)-((*S*)-2-Hydroxy-1,2,2-triphenylethylimino)-methyl)naphthalen-1-ol 5b. Mp 167 °C; $[\alpha]_D^{18} = -223$ (*c* 0.29, DMF); ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.95 (s, 1H), 8.92 (s, 1H), 8.20 (1, H), 7.84–7.82 (m, 3H), 7.60–7.43 (m, 5H), 7.35–6.85 (m, 11H), 5.68 (s, 1H), 5.60 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.6, 156.0, 146.6, 145.6, 141.4, 131.6.7, 129.5, 127.6, 127.3, 126.9, 126.4.1, 126.0, 124.8, 124.6, 124.3, 107.5, 80.2; MS (ESI): *m*/*z*: 444. IR (KBr): 3420, 3024, 2865, 1612, 1577, 1510, 1304, 1158, 1078, 755, 698, 467 cm^{-1}. Anal. Calcd for $C_{31}H_{25}NO_2$: C, 83.95; H, 5.68; N, 3.16. Found: C, 84.01, H, 5.63, N, 3.19.

4.1.3. 4-((*S*,*E*)-2-(Benzylideneamino)-3-hydroxy-3,3-diphenylpropyl)phenol 8a. Mp 223 °C; $[\alpha]_D^{18} = -196$ (*c* 6.5, THF); ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.10 (s, 1H, CH=N), 7.69–7.59 (m, 5H), 7.50–7.48 (m, 2H), 7.37–7.30 (m, 5H), 7.24–7.15 (m, 2H), 7.09–7.05 (m, 5H), 6.78–6.76 (d, 2H, $J = 8.4$ Hz), 6.57–6.55 (d, 2H, $J = 8.4$ Hz), 5.54 (s, 1H), 4.43–4.41 (m, 1H), 2.78–2.75 (m, 1H), 2.63–2.57 (m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.2, 155.3, 146.7, 146.1, 135.9, 130.4, 129.3, 128.4, 127.9, 127.7, 127.5, 126.7, 126.2, 126.0, 114.8, 78.5, 35.8. IR (KBr): 3537.8, 3487.0, 3020.2, 2889.7, 1635.8, 1513.6, 172.7, 756.2, 701.2 cm^{-1}; MS (ESI): *m*/*z*: 408.1 $[M+H]^+$. Anal. Calcd for $C_{28}H_{25}NO_2$: C, 82.53; H, 6.18; N, 3.44. Found: C, 82.46, H, 6.33, N, 3.41.

4.1.4. 4-((*S*,*E*)-2-((Anthracen-10-yl)methyleneamino)-3-hydroxy-3,3-diphenylpropyl)phenol 8b. Yellow crystal; mp 224–225 °C; $[\alpha]_D^{20} = +97$ (*c* 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (s, 1H, OH), 8.34 (s, 1H, CH=N), 7.88–7.84 (m, 6H), 7.45–7.0 (m, 8H), 7.13–7.09 (m, 2H), 7.05–7.02 (m, 2H), 6.89–6.87 (m, 2H), 6.77–6.75 (m, 2H), 5.03–4.92 (m, 1H), 4.23 (s, 1H), 3.07–2.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 154.2, 147.5, 144.1, 131.2, 131, 129.4, 129, 128.7, 128.5, 128.4, 126.8, 126.2, 126.1, 125.4, 125.1, 124.8, 115.8, 80.5, 35.7. IR (KBr): 3407, 3051, 2950, 2883, 1885, 1643, 1605, 1510, 1443, 1164, 959, 737, 699 cm^{-1}; MS (ESI): *m*/*z*: 508.3 $[M+1]^+$, 530.3 $[M+Na]^+$. Anal. Calcd for $C_{36}H_{29}NO_2$: C, 85.18; H, 5.76; N, 2.76. Found: C, 85.23, H, 5.78, N, 2.72.

4.2. Preparation of polymer-supported Schiff-base amino alcohols

A mixture of Schiff-base amino alcohol **8a** (1.22 g, 3 mmol), NaH (120 mg, 3 mmol), NBu_4I (115 mg, 0.3 mmol), and a small amount of 18C6 in dry THF (50 mL) was stirred at room temperature for 30 min. Subsequently, a 3 g Merrifield resin (1 mmol/g, 1% DVB, 200 mesh) was added, and the suspension refluxed for 60 h. The polymer was filtered and washed with THF, THF/H_2O, THF/MeOH, MeOH, CH_2Cl_2, Et_2O to give

polymer-supported Schiff-base amino alcohol **9a** containing 0.63 mmol of the functional group.

4.2.1. Compound **9a**: Elemental Anal. Found: C, 85.82; H, 7.44; N, 0.88. IR (KBr): 3485, 3025, 2922, 1645, 1603, 1505, 1448, 1237, 1174, 1023, 752, 697 cm^{-1}

4.2.2. Compound **9b** was used in the procedure above to give **9b**: Elemental Anal. Found: C, 87.01; H, 7.79; N, 0.83. IR (KBr): 3440, 3025, 2921, 1643, 1601, 1448, 1239, 1064, 754, 698, 536 cm^{-1}.

4.2.3. Compound **6a** was used in the procedure above to give **6a**: Elemental Anal. Found: C, 87.11; H, 6.96; N, 0.84. IR (KBr): 3442, 3025, 2920, 1643, 1602, 1448, 1230, 1024, 753, 697, 534 cm^{-1}.

4.2.4. Compound **6b** was used in the procedure above to give **6b**: Elemental Anal. Found: C, 86.67; H, 7.82; N, 0.87. IR (KBr): 3420, 3024, 2865, 1957, 1612, 1577, 1304, 1158, 755, 697, 467 cm^{-1}.

4.3. Experimental procedures

Under argon, ligand **9a** (40 mg, 0.025 mmol) was mixed in dry toluene (1.0 mL) at room temperature and stirred for 10 min. Then Et_2Zn in toluene (1.0 M, 0.5 mL) was added. Afterwards, phenylacetylene (54 μL, 0.05 mmol) was added. The mixture was stirred at room temperature for another 1 h, after which the solution was cooled to −18 °C and treated with ketones (0.25 mmol). The resulting mixture was stirred for 72–90 h at −18 °C. After the reaction was complete (monitoring with TLC), it was quenched with satd NH_4Cl. The mixture was then extracted with ether. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography to give the product.

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7. When dichloromethane was used for the reaction, the polymer became stuck on the inner wall of the round-bottomed flask upon stirring. However when hexane and toluene were used as solvents, the appearance disappeared.
8. Methyl isobutyl ketone (−18 °C in 1 mL toluene for 60 h, **9a**/Et_2Zn/phenylacetylene/ketones = 0.1:2:2:1, 39% ee, yield 81%).
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